Pediatric Neurology 53 (2015) 185–192

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Brain Injury in the Preterm Infant: New Horizons for Pathogenesis and Prevention

Stephen A. Back MD, PhD [a,b,*]

[a] *Department of Pediatrics, Oregon Health & Science University, Portland, Oregon*
[b] *Department of Neurology, Oregon Health & Science University, Portland, Oregon*

ABSTRACT

Preterm neonates are surviving with a milder spectrum of motor and cognitive disabilities that appear to be related to widespread disturbances in cell maturation that target cerebral gray and white matter. Whereas the preterm brain was previously at high risk for destructive lesions, preterm survivors now commonly display less severe injury that is associated with aberrant regeneration and repair responses that result in reduced cerebral growth. Impaired cerebral white matter growth is related to myelination disturbances that are initiated by acute death of premyelinating oligodendrocytes, but are followed by rapid regeneration of premyelinating oligodendrocytes that fail to normally mature to myelinating cells. Although immature neurons are more resistant to cell death than mature neurons, they display widespread disturbances in maturation of their dendritic arbors and synapses, which further contributes to impaired cerebral growth. Thus, even more mild cerebral injury involves disrupted repair mechanisms in which neurons and premyelinating oligodendrocytes fail to fully mature during a critical window in development of neural circuitry. These recently recognized distinct forms of cerebral gray and white matter dysmaturation raise new diagnostic challenges and suggest new therapeutic strategies to promote brain growth and repair.

Keywords: hypoxia-ischemia, prematurity, white matter, gray matter, myelination, oligodendrocyte, astrocyte, glia

Pediatr Neurol 2015; 53: 185-192

Neurodevelopmental disabilities continue to be a leading cause of morbidity in survivors of premature birth[1-11] and persists at very high rates throughout life.[12] Although improved neonatal intensive care has reduced the mortality of preterm neonates, 5%-10% of preterm survivors continue to have major motor deficits, including cerebral palsy, and more than half have significant cognitive, behavioral, or sensory deficits. This broad range of disabilities is consistent with widely distributed brain abnormalities or problems with brain connectivity.[13] Preterm children with IQ in the normal range, often display processing deficits related to attention and executive functions that include cognitive flexibility, inhibitory control and working memory[3,14,15] as well as deficits in visually based information processing and language.[16-21] Frequently, these cognitive and behavior problems persist to young adulthood.[8-10,19,20,22,23]

Given this broad spectrum of disabilities, how should neurorehabilitation be approached to improve the outcome for these children? This review will address this challenging and unresolved question by examining unexpected recent changes in our understanding of the pathogenesis of brain injury in preterm neonates. Whereas preterm infants were previously at high risk for destructive white and gray matter degeneration, preterm survivors now commonly display less severe injury that does not appear to involve pronounced glial or neuronal loss. Nevertheless, these milder forms of injury are associated with reduced cerebral

Article History:
Received February 26, 2015; Accepted in final form April 12, 2015

* Communications should be addressed to: Dr. Back; Clyde and Elda Munson Professor of Pediatric Research; Division of Pediatric Neuroscience; Department of Pediatrics; Oregon Health and Science University; 3181 S.W. Sam Jackson Park Rd; Mail Code L481; Portland, OR 97239-3098.
E-mail address: backs@ohsu.edu

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http://dx.doi.org/10.1016/j.pediatrneurol.2015.04.006

growth. Recent human and experimental studies support that this impaired cerebral growth involves abnormal maturation of neurons and glia rather than cell death. These complex and disparate cellular responses result in large numbers of cells that fail to fully mature during a critical window in the development of neural circuitry. These recently recognized forms of cerebral gray and white matter dysmaturation raise new diagnostic challenges and suggest new therapeutic directions centered on reversal of the processes that promote dysmaturation.

Pathogenesis of white matter injury

The changing spectrum of white matter injury in contemporary preterm survivors

In prior decades, preterm infants were at much higher risk for destructive brain lesions that resulted in cystic necrotic white matter injury (WMI) and secondary cortical and subcortical gray matter degeneration. Whereas cystic lesions were previously the major form of WMI in preterm survivors, the incidence has markedly declined.[24-27] In several recent series, focal cystic lesions were detected by magnetic resonance imaging (MRI) in fewer than 5% of patients.[24-29] More commonly, a milder spectrum of WMI is seen that is characterized by two distinct forms of injury (Fig 1). The minor component of WMI comprises small discrete foci of microscopic necrosis (microcysts) that typically measure less than a millimeter.[30] Because of their relatively small size, microcysts are occult lesions that are typically not detected by MRI. Although microcysts have been observed in ~35% of autopsy cases, they comprised only ~1%-5% of total lesion burden.[31] Moreover, the overall burden of human necrotic WMI (cystic and microcystic) decreased by ~10-fold in contemporary cohorts relative to retrospective cases from earlier decades.[31] Essentially complete myelination failure occurs in these relatively uncommon but clinically significant necrotic lesions as a consequence of the degeneration of all cellular elements.

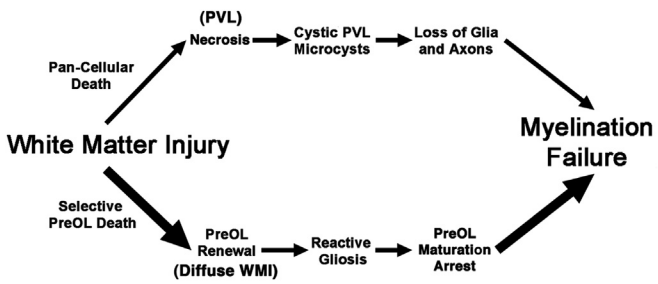

FIGURE 1.
Pathogenesis of myelination failure arising from white matter injury (WMI) related to pan-cellular death and necrosis (periventricular leukomalacia (PVL); upper pathway) or selective premyelinating oligodendrocyte (preOL) death and diffuse WMI (lower pathway). Note that the lower pathway is the dominant one in most contemporary preterm survivors, whereas the minor upper pathway reflects the declining burden of white matter necrosis that has accompanied advances in neonatal intensive care. Severe necrosis results in macrocystic lesions (cystic PVL), whereas milder necrosis results in microcysts. Milder WMI selectively triggers early preOL death. PreOLs renewal arises from the rapid regeneration of preOLs from a pool of early OL progenitors that are much more resistant to cell death in WMI. Chronic lesions are enriched in reactive astrocytes that generate inhibitory signals that block the maturation of preOLs to mature myelinating oligodendrocytes.

Diffuse WMI is currently the most frequently observed form of WMI in premature newborns. Diffuse WMI evolves from early lesions where the oligodendrocyte (OL) lineage is particularly susceptible to oxidative damage[32] of a magnitude consistent with hypoxia-ischemia.[33,34] Initially, diffuse WMI causes widespread selective degeneration of late OL progenitors (preOLs) in premyelinating white matter. Axons are mostly spared in premyelinating white matter[35] except in necrotic foci.[36,37] At the onset of myelination, axons expand in caliber and display increased susceptibility to oxidative stress and hypoxia-ischemia.[38-40] Hence, disturbances in myelination are initiated by "selective vulnerability" of preOLs that are enriched in human cerebral white matter during the high-risk period for WMI.[41]

In about one-third of preterm newborns at 24-32 weeks' gestation, diffuse WMI is readily identified on MRI as multifocal lesions in the first weeks of life.[1,42] Although MRI-defined focal lesions are associated with increased risk for neurocognitive and motor dysfunction, they likely underestimate the extent of WMI and the burden of neurodevelopmental disability.[1,43-46] As premature newborns grow to term age, early multifocal lesions give rise to more widespread abnormalities in microstructural and metabolic brain development.[42,47-49] The consequence is adverse long-term neurodevelopmental outcomes, which are associated with disrupted white matter maturation that manifests in childhood as altered brain structure and connectivity.[13,44,50-55]

Abnormal myelination in diffuse white matter injury is mediated by degeneration and dysmaturation of preOLs

PreOLs predominate in human cerebral white matter throughout the high-risk period for WMI and are the primary cell type that degenerates in early WMI in the setting of hypoxia-ischemia or inflammation.[32,56,57] Subsequently, abnormal myelination occurs via a process that involves a more complex and potentially reversible process linked to arrested preOL maturation. Several studies found, paradoxically, that although pronounced extensive degeneration of preOLs occurs in acute lesions, no significant depletion of OL lineage cells was observed in chronic human or experimental lesions.[31,58-61] This is related to the fact that developing white matter is populated by a large reservoir of early OL progenitors that are resistant to hypoxia-ischemia and proliferate robustly in the setting of preOL degeneration.[33] Thus, after WMI, developing white matter is capable of engaging repair mechanisms that trigger the rapid regeneration and pronounced expansion of preOLs that derive from early OL progenitors.[58,62,63] Although regeneration of preOLs compensates for preOL death, these newly generated preOLs display persistent arrested differentiation in chronic lesions and fail to myelinate intact axons. Arrested maturation of preOLs was shown to contribute to myelination failure in diffuse WMI in both preterm fetal sheep and human WMI.[31,60] Hence, chronic diffuse